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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,717	07/24/2001	Jennifer L. Hillman	PF-0532-2 DIV	5873

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INCYTE GENOMICS, INC.
PATENT DEPARTMENT
3160 Porter Drive
Palo Alto, CA 94304

EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	5

DATE MAILED: 03/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,717	HILLMAN ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 28-44* is/are pending in the application.

4a) Of the above claim(s) *1-3,29,32, 34,43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,30,31,33 and 35-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Group 1640, Technology Center 1600.

2. Claims 1-3, and 28-44 are pending.

Election/Restrictions

3. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-2, drawn to polypeptide comprising the amino acid sequence of SEQ ID NO: 1, classified in Class 530, subclass 350.

II. Claim 3, drawn to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, classified in Class 536, subclass 23.2.

III. Claims 28, 30-31, 33 and 35-42, drawn to an isolated antibody that binds to a polypeptide of SEQ ID NO: 1, a composition comprising said antibody, and a method of making said antibody, classified in Class 424, subclass 130.1.

IV. Claims 32 and 34, drawn to a method of diagnosing a condition or disease associated with the expression of P5CRH comprising administering to a subject an effective amount of an antibody that binds to a polypeptide of SEQ ID NO: 1, classified in Class 424, subclass 9.1.

V. Claims 29 and 43, drawn to a diagnostic test for a condition or disease and a method for detecting a polypeptide using antibody that binds to polypeptide of SEQ ID NO: 1, classified in Class 435, subclass 7.1.

VI. Claim 44, drawn to a method of purifying a polypeptide using antibody that binds to a polypeptide of SEQ ID NO: 1, classified in Class 530, subclass 413.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Group III and Groups (IV-VI) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different

product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the products as claimed can be used in materially different process such as the three different uses in Groups IV-VI. Therefore, they are patentably distinct.

Inventions of Groups I-III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the products (polypeptide, polynucleotide versus antibody) as claimed differ with respect to structure and physiochemical properties. Therefore, they are patentably distinct.

Inventions of Groups IV-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the methods of detecting a polypeptide in vitro versus in vivo and a method of purifying polypeptide differ with their respect to their process steps and endpoints. Therefore, they are patentably distinct.

4. Because these inventions are distinct for the reasons given above and the searches are not co-extensive, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Dr. David Streeter on 01/30/02 a provisional election was made with traverse to prosecute the invention of Group III, drawn to an antibody. Affirmation of this election must be made by applicant in replying to this Office Action. Claims 1-3, 29, 32, 34, 43 and 44 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

7. Claims 28, 30-31, 33 and 35-42 are being acted upon in this Office Action.

8. Applicant should amend the first line of the specification to update the relationship between the instant application and 09/565,910, filed 5/5/2000, which is now Pat No. 6,268,192, which is a Div of 09/099,676, filed 6/18/1998, which is now Pat No. 6,100,075.

9. Claims 28, 30-31, 33 and 35-42 are objected because the claims depend on non-elected claim 1.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 28, 30-31, 33 and 35-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated antibody which specifically binds to a purified polypeptide comprising an amino acid sequence of SEQ ID NO: 1; (2) A method of preparing a polyclonal antibody with the specificity of an isolated antibody which specifically binds to a purified polypeptide comprising an amino acid sequence of SEQ ID NO: 1 comprising a) immunizing an animal with a polypeptide consisting of SEQ ID NO: 1, under the conditions to elicit an antibody response; b) isolating antibodies from said animal and c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide consisting of SEQ IDNO: 1; (3) An isolated antibody produced by preparing a polyclonal antibody with the specificity of an isolated antibody which specifically binds to a purified polypeptide comprising an amino acid sequence of SEQ ID NO: 1 comprising a) immunizing an animal with a polypeptide consisting of SEQ ID NO: 1 under the conditions to elicit an antibody response; b) isolating antibodies from said animal and c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide consisting of SEQ IDNO: 1; (4) A method of making a monoclonal antibody comprising a) immunizing an animal with a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 under the conditions to elicit an antibody response, b) isolating antibody producing cells from the animal; c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells; d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide consisting of amino acid sequence of SEQ ID NO: 1; (5) A monoclonal antibody produced by a) immunizing an animal with a polypeptide consisting of an amino acid sequence of

SEQ ID NO: 1 under the conditions to elicit an antibody response, b) isolating antibody producing cells from the animal; c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells; d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide consisting of amino acid sequence of SEQ ID NO: 1 and (6) An isolated antibody specifically binds to a purified polypeptide comprising an amino acid sequence of SEQ ID NO: 1 produced by screening a recombinant library or by screening a recombinant immunoglobulin library for diagnostic assays, does not reasonably provide enablement for (1) *any* isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1; (2) *any* composition comprising *any* antibody mentioned above and an acceptable excipient for treating *any* disease; (3) A method of preparing a polyclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1; (4) *any* isolated antibody produced by a) immunizing an animal with a polypeptide having an amino acid sequence of SEQ ID NO: 1 or an immunogenic fragment thereof, under the conditions to elicit an antibody response; b) isolating antibodies from said animal and c) screening the isolated antibodies with *any* polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1; (5) *any* composition comprising *any* polyclonal antibody mentioned above and a suitable carrier for treating any disease; (6) A method of making *any* monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) any immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 comprising the steps as recited in claim 38; (7) *any* monoclonal antibody produced by the method mentioned above; (8) *any* composition comprising any monoclonal antibody mentioned above

and a suitable carrier for treating *any* disease and (9) *any* antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only an isolated antibody which specifically binds to a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody and a method of producing said antibody for diagnostic and detection assays (See page 19, lines 26-34, pages 24-25, 44).

The specification does not teach how to make and use *any* antibody that binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide "having" the amino acid sequence of SEQ ID NO: 1, c) *any* immunogenic fragment of the polypeptide "having" an amino acid sequence of SEQ ID NO: 1 since neither the structure nor function of *any* amino acid sequence mentioned above is provided. Furthermore, the term "having" is open-ended. It expands the polypeptide fragment to include additional amino acid residues at either end. Given the indefinite number of undisclosed amino acid sequence and polypeptide fragment thereof, there is insufficient guidance in the specification as to the structure associated with functional properties of said polypeptide, biochemical

information such as the specific amino acids residues used as an immunogen, epitopes and antibody binding specificity, it is unpredictable that immunizing with an undisclosed amino acid sequence and polypeptide fragment will have the same antibody specificity as the antibody that binds specifically to SEQ ID NO: 1, in turn, would be useful for any purpose.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimentional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable to determine which antibody generated from a naturally-occurring amino acid sequence such as having 90% sequence identity to SEQ ID NO: 1 or fragment thereof "having" an amino acid sequence of SEQ ID NO: 1 will have the same antibody specificity as an antibody generated from the full-length polypeptide consisting of the amino acid sequence of SEQ ID NO: 1. Since the amino acid sequence and specificity of said antibody is not enabled, it follows that the method of making any antibody using any undisclosed amino acid sequence, biologically active fragment of the polypeptide and any immunogenic fragment having the amino acid sequence of SEQ ID NO: 1 is not enabled.

With regard to composition comprising any polyclonal or monoclonal antibody and an acceptable excipient or suitable carrier as recited in claim 31, 37 and 40, the specification fails to provide any *in vivo* working examples, or guidance with respect to treating a patient suffering from *any* disease using *any* antibody mentioned above. Given the indefinite number of disease, the lack of guidance and in vivo working examples, further research is required. Since the composition comprising said antibody is not enabled, it follows that composition comprising the labeled antibody is not enabled.

The '370 patent teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular). In the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as serum sickness which prohibitive to the use of antibody for such

treatment. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

12. Claims 28, 30-31, 33 and 35-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1; (2) *any* composition comprising *any* antibody mentioned above and an acceptable excipient for treating *any* disease; (3) A method of preparing a polyclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1; (4) *any* isolated antibody produced by a) immunizing an animal with a polypeptide having an amino acid sequence of SEQ ID NO: 1 or an immunogenic fragment thereof, under the conditions to elicit an antibody response; b) isolating antibodies from said animal and c) screening the isolated antibodies with *any* polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1; (5) *any* composition comprising *any* polyclonal antibody mentioned above and a suitable carrier for treating any disease; (6) A method of making *any*

monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) any immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 comprising the steps as recited in claim 38; (7) *any* monoclonal antibody produced by the method mentioned above; (8) *any* composition comprising any monoclonal antibody mentioned above and a suitable carrier for treating *any* disease and (9) *any* antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library.

The specification discloses only an isolated antibody which specifically binds to a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 or an immunogenic fragment thereof wherein the antibody is a chimeric antibody, a single chain antibody, a humanized antibody, a Fab fragment, a F(ab')2 fragment thereof and a method of producing said antibody for diagnostic and detection assays (See page 19, lines 26-34, pages 24-25, 44).

With the exception of the specific antibody that binds to a polypeptide consisting of SEQ ID NO: 1, there is insufficient written description about the structure associated with function of an isolated antibody that binds to (1) *any* naturally-occurring amino acid sequence "having" at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1, (2) *any* biologically active fragment of the polypeptide "having" the amino acid sequence of SEQ ID NO: 1, (3) *any* immunogenic fragment of the polypeptide "having" an amino acid sequence of SEQ ID NO: 1 for in vivo treatment of any disease and diagnostic assays.

Given the lack of a written description of *any* additional representative species of polypeptide other than the polypeptide of SEQ ID NO: 1 to which the antibody binds wherein the antibody is polyclonal, monoclonal, chimeric, humanized, Fab fragment, F(ab')2 fragment thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 28, 31, 33 and 35-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7 and 8 of U.S. Patent No. 6,268,192 B (July 2001, PTO 892). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons:

(1) Claim 7 of the '192 patent recites a method of using a protein to make a polyclonal antibody, the method comprising immunizing an animal with a protein comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1 and which retains delta 1-pyrroline-5-carboxylate reductase activity. Therefore, claim 7 of the '192 patent includes the limitation in the instant claim 35 which recites a method of preparing a polyclonal antibody with the specificity of the antibody comprising immunizing an animal with a polypeptide comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1. Note, the immunogen is the same protein wherein the delta 1-pyrroline-5-carboxylate reductase activity is the inherent functional property of said protein.

Further, the method of making polyclonal antibody using said immunogen as evidence in the instant specification on page 44, lines 13-28 is the same as the '192 patent.

(2) Claim 8 of the '192 patent recites a method of using a protein to make a monoclonal antibody, the method comprising immunizing an animal with a polypeptide comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1 and which retains delta 1-pyrroline-5-carboxylate reductase activity. Therefore, claim 8 of the '192 patent includes the limitation in the instant claim 38 which recites a method of preparing a monoclonal antibody with the specificity of the antibody comprising immunizing an animal with a polypeptide comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1. Note, the immunogen is the same protein wherein the delta 1-pyrroline-5-carboxylate reductase activity is the inherent functional property of said protein. Further, the method of making polyclonal antibody using said immunogen as evidence in the instant specification on page 44, lines 13-28 is the same as the '192 patent.

(3) Claim 1 of the '192 patent recites an isolated polypeptide comprising an amino acid sequence selected from the group consisting of: (a) an amino acid sequence of SEQ ID NO: 1, and (b) an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1, and which retains delta 1-pyrroline-5-carboxylate reductase activity which includes claim 1(a) and (b) of instant application since the delta 1-pyrroline-5-carboxylate reductase activity is the inherent functional property of claimed polypeptide.

(4) Claims 36 and 39 are included in this rejection because the antibody produced by a method as taught by the '192 patent discussed supra.

(5) Claims 31, 33, 37 and 40 are included in this rejection because the claimed antibody in the composition is the same antibody produced by the method as taught the '192 patent as discussed supra.

15. Claims 30 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7 and 8 of U.S. Patent No. 6,268,192 B (July 2001, PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629, 342-345).

The teachings of the '192 patent have been discussed supra.

The claimed invention in claim 30 differs from the reference only by the recitation of the antibody is a Fab fragment, or a F(ab')2 fragment.

The claimed invention in claim 33 differs from the reference only by the recitation of the antibody is labeled.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* teach a method of labeling antibodies with an enzyme for various immunoassays and the advantage of labeling with an enzyme is due to the intrinsic amplification of the signal by the enzyme reaction, even the relatively poor conjugates available can prove exceptionally sensitive (See page 342-345, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make the Fab and F(ab')2 fragment or label antibody as taught by Harlow *et al* that binds specifically to a polypeptide comprising a naturally occurring amino acid sequence having 90% identity to the claimed amino acid sequence of SEQ ID NO: 1 as taught by the '192 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Harlow *et al* teach the Fab or F(ab')2 antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies as taught by Harlow et al (See page 626 in particular) and the advantage of labeling antibody with an enzyme is due to the intrinsic amplification of the signal by the enzyme reaction, even the relatively poor conjugates available can prove exceptionally sensitive (See page 342-345, in particular).

16. Claims 30 and 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7 and 8 of U.S. Patent No. 6,268,192 B (July 2001, PTO 892) in view of US Pat 6,180,370 B (; PTO 892).

The teachings of the '192 patent have been discussed supra.

The claimed invention in claim 30 differs from the reference only by the recitation of the antibody is a chimeric antibody or a humanized antibody.

The claimed invention in claim 41 differs from the reference only by the recitation of the antibody is produced by screening a Fab expression library.

The claimed invention in claim 42 differs from the reference only by the recitation of the antibody is produced by screening a recombinant immunoglobulin library.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular) by screening a Fab expression library or a recombinant immunoglobulin library. The reference chimeric antibody comprising a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody or humanized antibody as taught by the '370 patent that binds specifically to the polypeptide as taught by the '192 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

17. Claim 30 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7 and 8 of U.S. Patent No. 6,268,192 B (July 2001, PTO 892) in view of US Pat No. 4,946,778; PTO 892).

The teachings of the '192 patent have been discussed supra.

The claimed invention in claim 30 differs from the reference only by the recitation of the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody or a polypeptide fragment (See column 29, lines 25 bridging

column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent that binds specifically to the polypeptide as taught by the '192 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
March 11, 2002

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640